

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 50-785

CORRESPONDENCE

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APR 18 2002

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GlaxoSmithKline

April 17, 2002

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation IV
Attn: Document Control Room
Food and Drug Administration
Corporate Building / HFD-520
9201 Corporate Boulevard
Rockville, MD 20850

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APR 23 2002

MEGA/CDER

GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929
Tel. 215 751 3868
Fax. 215 751 4926

**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets
Amendment to Pending Application: Additional Case Report Forms**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham's resubmission on March 29, 2002 of the New Drug Application (NDA 50-785) for Augmentin XR™ (amoxicillin/clavulanate potassium) Extended Release Tablets. SmithKline Beecham is a wholly owned subsidiary of GlaxoSmithKline (GSK).

Please also refer to the teleconference of March 21, 2002 between representatives of GSK and the Division of Anti-Infective Drug Products (DAIDP) in which GSK agreed to provide selected Case Report Forms (CRFs) to the Division by April 19, 2002. All of the selected CRFs are provided in this amendment, and the individual categories are summarized below.

- CRFs for all patients who had severe CAP, as defined by modified Fine class IV or V (n=216)
- CRFs for all patients who received corrective therapy related to diarrhea, abdominal pain, nausea or vomiting that were reported as severe adverse events (n=35)
- CRFs for all patients who received more than symptomatic treatment, i.e., antibiotics, IV fluids, endoscopic or radiological procedures, as corrective therapy related to the GI adverse events noted above (n=21)
- CRFs for all patients who received corrective therapy related to the adverse event of genital moniliasis (87 patients)

ORIGINAL

Janice Soreth, M.D.

April 17, 2002

Page 2

- CRFs for a randomly selected sample of 30 patients from each of two treatment groups in Study 557

Because patients are represented in more than one of the above categories, a total of 403 CRFs are provided. In addition, the statistical documentation for the generation of the randomly selected sample of patients from 557 is provided in Portable Document Format:

- the SAS code used to generate the random sample – *select_crf(code)*
- the list of patients generated, including the "seed" for the sample – *select_crf(output)* and
- the associated log for the output above – *select_crf(log)*

This amendment is provided electronically on a single DLT Tape. If you have any questions or requests regarding this application, please contact me at 215-751-3468 (phone) or 215-751-4926 (fax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.

Director

U.S. Regulatory Affairs

Copies: Archival (1 DLT Tape)

**APPEARS THIS WAY
ON ORIGINAL**

April 30, 2002

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MAY 06 2002

MEGA/CDER

NDA ORIG AMENDMENT



GlaxoSmithKline

Mathew Thomas, M.D., Scientific Review Officer
Division of Scientific Investigations
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Office of Scientific Investigations
Food and Drug Administration
HFD-344, Metro Park North 1
7520 Standish Place
Rockville, MD 20855

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MAY 01 2002

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Fax. 215 751 4926

**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets
Response to FDA Request/Comment**

Dear Dr. Thomas:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for Augmentin XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

At this time, we are providing information for three Phase III studies of Augmentin XR that were included in the March 29, 2002 resubmission: community-acquired pneumonia - studies 547 (2nd interim report) and 557, and acute bacterial sinusitis - study 592. The information corresponds to that which was provided on April 12, 2001 for clinical studies in the original NDA, as described below.

- The name and address of principal investigators by study (Table 10.01 from each clinical study report);
- The list of CROs used for monitoring or auditing by study (extracted from section 3.12 in each clinical study report);
- The list of audited sites and dates of the audits by study (extracted from Appendix A in each clinical study report);
- The protocol synopsis for each study (extracted from Appendix A in each clinical study report);

Mathew Thomas, M.D.

April 30, 2002

Page 2

- The number of patients enrolled (all enrolled patients were assigned a randomization number); clinically evaluable for safety (Clinical ITT), clinically evaluable for efficacy (Clinical PP), microbiologically evaluable (Bacteriology ITT and PP), and completed by investigator for each study (Biometrics Table 10.03.X for each study);
- The number of patients who reported an adverse event and the total number of patients who reported adverse events by investigator for each study (Biometrics Table 12.45.X or Table 12.46.X, depending upon study).

This information is being provided in electronic format in duplicate; a paper review copy is also included. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.

Director

U.S. Regulatory Affairs

Copies: Original (1 copy on CD-ROM)

Archival (1 copy on CD-ROM);

Review copy – Dr. Mathew Thomas (HFD-45)

Desk copy (cover memo only) – Dr. Susmita Samanta (HFD-520)

**APPEARS THIS WAY
ON ORIGINAL**

SPONSOR MEETING MINUTES

Meeting Date: June 7, 2000

Location: Corporate Building -Room S-300

IND: _____

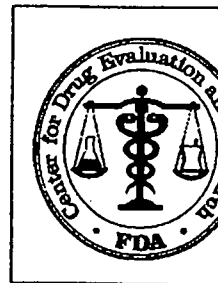
Drug: Augmentin[®] (amoxicillin/clavulanate potassium)

Sponsor: SmithKline Beecham Pharmaceuticals

Type of Meeting: Pre-NDA

Meeting Chair: Gary Chikami, M.D.
Division Director
Division of Anti-infective Drug Products (HFD-520)

Minutes Recorder: Susmita Samanta/ Project Manager



FDA Attendees:

Titles:

Offices:

Gary Chikami, M.D.	Division Director	HFD-520
Mercedes Albuerno, M.D.	Medical Team Leader	HFD-520
Frank Pelsor, Ph.D.	Team Leader/Clinical Pharmacology	HFD-520
Sousan Altaie, Ph.D.	Microbiology Reviewer	HFD-520
Erica Brittain, Ph.D.	Biometrics Reviewer	HFD-520
David Katague, Ph.D.	Chemistry Team Leader	HFD-520
Mamodikoe Makhene, M.D.	Clinical Reviewer	HFD-520
Robert Osterberg, Ph.D.	Pharmacology Team Leader	HFD-520
Ken Seethaler, Ph.D.	Pharmacology Reviewer	HFD-520
Cdr. Jose Cintron	Project Manager	HFD-520
Dr. Susmita Samanta	Project Manager	HFD-520

SmithKline Beecham Attendees:

Titles:

Dr. Cynthia D'Ambrosio	Associate Director, US Regulatory Affairs
Ms. Jane Finlay	Associate Investigator, Clinical Microbiology
Ms. Regina Jurewicz	Assistant Director, Clinical Research
Dr. Clive Kaye	Director, DMPK
Ms. Claire Lockwood	Senior Statistician, Biometrics
Mr. Charles McGovern	Assistant Director, Electronic Submissions
Dr. Robert Pietrusko	Vice President, US Regulatory Affairs
Dr. Robin Saltzman	Group Director, Clinical Research
Mr. David Rawlinson	Associate Director, Clinical Research
Dr. Karen Wells	Associate Director, Biometrics
Dr. Gary Woodnutt	Director, Microbiology

Dr. Brian Wynne
Dr. Marie-Paule Richard

Associate Director, Clinical research
Group Director, Clinical Research

Background Information:

The Sponsor plans to submit an NDA in December, 2000 to provide for the use of a sustained-release formulation of Augmentin® (Augmentin —) in the treatment of selected respiratory tract infections. The Sponsor requested a pre-NDA meeting with the Division a) to obtain agreement on general organization of the NDA with specific emphasis on the proposed organization of the ISE, ISS and Microbiology items and b) to obtain agreement on which NDA elements can be submitted in electronic format only. The briefing document was received on May 9, 2000. The Division needed clarification for two questions the responses to which were received at the Division on June 5, 2000.

Discussion Points:

After introduction of the meeting attendees, the Sponsor provided an agenda and brief introduction of the product. The Phase III formulation was described as containing 2000/125 mg amoxicillin/clavulanate potassium in a bilayer tablet with immediate release — and sustained release — layers. The proposed indications were 1) acute bacterial sinusitis (ABS), — and community-acquired pneumonia (CAP), including infections due to penicillin-resistant and macrolide-resistant strains of *S. pneumoniae*. In addition, the Sponsor noted that where applicable, indications would ask for methicillin susceptible *S. aureus* only. The Sponsor added that there were no new pharmacology/toxicology studies. The NDA would contain 3 new biopharmaceutics studies-bioavailability, food effect and antacid interaction studies. The following questions (in *italics*) were then discussed:

1. *Because the preclinical safety of the components of Augmentin — has been evaluated and submitted previously, SB plans to incorporate this information by reference. Is this acceptable?*

The Division indicated that this is acceptable.

2. *Is the clinical pharmacokinetic information in Item 6, as outlined in the draft index, acceptable for review and approval?*

The Division asked if steady-state was achieved after a single dose. The Sponsor responded that it was. The phase I program was agreed to be acceptable.

3. *SB proposes to provide CRFs for patients who died, had a serious adverse event or withdrew due to an adverse event. Is this acceptable to the division?*

The Division responded that it is acceptable, however, indicated that they would reserve the right to request additional CRFs after the NDA is submitted.

4. *Does the Division agree with our strategy and timing for addressing the Pediatric Rule?*

The Sponsor's proposal contained three parts:

[]

The Division requested the details of the timing and studies to be performed with respect to the deferrals. The Division expressed concern about the size of the tablet and felt that a safety and tolerability study was needed. The Sponsor indicated that the time line for studies, _____ issue will be provided when the NDA is filed.

5. *Since no product is currently approved for the treatment of acute bacterial sinusitis due to penicillin-resistant S.pneumoniae, SB plans to request a priority review for this application based on the unmet clinical need in this population.*

The Division stated that the development program did not meet all of the criteria for a priority review since the approach was an all-comers approach, not specifically targeted to PRSP. The standard review time for this indication will be 10 months. The Sponsor indicated that rationale for priority review would be provided at the time of NDA filing.

6. *Prior to breaking the codes for blinded studies, SB will review all patients who were protocol violators. Only those that were considered to impact the assessment of efficacy will be formally excluded from the per protocol analyses. Does the Division agree with this approach?*

Although the approach is acceptable, the Division requested documentation on how the assessment was made. Specifically, the Division would like to be able to compare the totality of strict protocol violators with those that were identified by the Sponsor as impacting efficacy. The Sponsor agreed.

7. *Does the Division agree that the proposed efficacy analyses are appropriate, as they are consistent with the AI Division guidelines?*

The Division stated that the statistical goal is not enough in the evaluation of efficacy. The Division is no longer using the approach of the 1992 Points-to-Consider document with respect to deltas. The Division would not normally accept a delta of more than 5-10% under the new approach. The Sponsor must

consider a variety of factors such as, disease being studied, consequences and the significance of treatment failure in the particular indication. The Sponsor should consult Advisory Committee discussions and draft guidances on this issue. In addition, the Division noted that the results of the analyses for both the ITT and PP populations are important and should be evaluated for consistency. The Division pointed out that the test-of-cure (TOC) window in the CAP studies was one week beyond that recommended in the AI guidance document for this indication.

8. *As per previous agreement with the Division, SB plans to base the PRSP claim for acute bacterial sinusitis (ABS) on data from Augmentin® — study 551 and the Augmentin® ES acute otitis media study 536. The data for patients with S. pneumoniae isolates will be pooled across these studies for both clinical and bacteriological results (including 95% confidence intervals) and presented according to the level of penicillin resistance. Does the Division agree with this approach?*

The Division agreed that this is acceptable, as previously discussed and agreed to at the End-of-Phase 2 meeting.

9. *SB plans to base PRSP claims for CAP: — by pooling the results for patients with S. pneumoniae isolates from the Augmentin® - studies in CAP — Does the Division agree with this approach?*

The Division stated that the primary evidence of efficacy against resistant isolates should be demonstrated in CAP patients. Within the CAP population, patients with bacteremia are considered particularly important, as well as patients with severe CAP, as they provided the most convincing data of efficacy. More weight will be placed on the CAP studies because they are associated with more serious infections.

10. *Does the Division have any comments or recommendations on the proposed table of contents and sample data tables in the ISS?*

The Division indicated that the overall format and content are acceptable. However, the Division would like to obtain separate safety analyses for the individual comparative agents. The combined levofloxacin comparative studies are of particular interest.

11. *SB plans to provide an integrated safety analysis across all indications regardless of the duration of treatment (7d or 10d). Does the Division agree with this approach?*

The approach is acceptable.

12. *Most in vitro data in previous Augmentin submissions (e.g., mechanism of action) are applicable to Augmentin — therefore they will not be reproduced in this submission. Is that acceptable?*

The Division would like to see the development of resistance studies with recent (not >5 years old) clinical isolates of *S.pneumoniae*, *H.influenzae* and *M.catarrhalis*. These studies should be done using serial passage methodology. Also, spontaneous mutation frequencies for the key pathogens could be conducted, but were not essential.

13. *SB proposes to present the MIC frequency distributions for in vitro surveillance studies for the geographic regions: US, Europe and Global, and the clinical and bacteriological efficacy data by MIC for the geographic regions: US, non-US and Global. Does the Division agree with this approach?*

The regions are acceptable.

14. *The proposed susceptible breakpoint for S.pneumoniae will be supported by MIC frequency distributions, the $T > MIC$ (PK/PD) parameter, the results of in vivo animal studies and the available clinical/bacteriological efficacy against isolates with MIC's \geq breakpoint. Does the Division agree with this general approach?*

The Division indicated that the approach is generally acceptable. The Sponsor should include scattergrams/frequency distributions for both clinical and in vitro surveillance isolates. Frequency distributions from the clinical and in vitro surveillance studies could be "overlayed" to assist in the comparison and to look for shifts between the two populations.

15. *Does the Division agree that, for amoxicillin, a $T > MIC$ approaching 40% of the dosing interval is correlated with an adequate and clinically meaningful efficacy rate in humans?*

The Division considered a $T > MIC$ of 40% as a "starting point" for breakpoint evaluation, and much more emphasis is placed upon observed clinical efficacy. The Sponsor agreed to provide full documentation in the NDA in support of the $T > MIC$ approaching 40%.

16. *SB proposes to combine the clinical/bacteriological efficacy for all Augmentin — RTI studies, except 550 (ABS-no sinus puncture) and 556 (CAP-10d treatment) at the TOC visit and for Augmentin ES study 536 (AOM) at the on-therapy visit (bacteriological) and EOT visit (clinical). Separate analyses will be presented for the PP and ITT populations. Does the Division agree with this approach?*

The Division indicated that the proposal is acceptable.

17. *SB has proposed to provide the full archival submission in electronic format. Does the Division have any concerns with the proposal?*

The proposal is acceptable.

18. *Is our proposal to provide printed review copies of selected portions of the submissions acceptable to the Division?*

The proposal is acceptable.

19. *To comply with the requirement for CRTs, SB is planning to provide SAS transport files. Is this acceptable to the Division? Will this meet the needs of both the statistical and medical reviewers? Does the Division require that SB provide integrated datasets in addition to the individual study datasets?*

The proposal to provide SAS transport files for the clinical studies was acceptable. The Division indicated that it would meet the needs of both the medical and statistical reviewers. In addition, the Division indicated that a master variables listing file would be helpful. Integrated datasets are helpful tools. The Division recently requested a dataset for Augmentin ES and suggested that similar datasets be submitted for Augmentin.

20. *Three pharmacokinetic studies will be included in this NDA. Are there any specific requirements for the submission and structure of datasets to support the review of these studies?*

No preference indicated.

21. *In light of our proposal to provide SAS transport files, what types of applications will the reviewers use to review and query the datasets (e.g., Access, SAS JMP, etc.)? As SB is providing SAS datasets for review and analysis, is it necessary to also provide Patient Profiles as a review aid?*

The Division indicated that SAS JMP will be used as the query tool. Patient profiles would be helpful for clinical review.

Note: Although not discussed at the meeting, the guidance document indicates that patient profiles should be provided as part of archival submission, not as a review aid.

22. *SB anticipates working with the Division to support the review team in the use of SAS transport files. At what point in the submission/review process does the Division feel the assistance might be most valuable?*

The Division indicated that assistance could be provided on an "as needed" basis during the review.

23. *The guidance indicates that submission of programs used in statistical analyses is optional. Does the Division see a need for submission of the programming code detailing the analysis of the Augmentin — efficacy (or safety) data?*

The Division indicated that submission of the programming code is desirable.

24. *We would like to set up secure communications with the Division to exchange documents, questions, labeling via the FDA secure communication pilot. What are the Division's experience and preference in this domain?*

The Division expressed an interest in establishing a secure link for the review of this application. This would be especially useful during final labeling negotiations. It was noted that all communications via the electronic link are not considered official communication, and that all official communication needed to be submitted formally to the NDA.

The discussion was concluded and the meeting adjourned.

Minutes Prepared By: S. Samanta, /S/

Minutes Concurred By: Gary Chikami, M.D. /S/ *for Gary Chikami*

**APPEARS THIS WAY
ON ORIGINAL**

NDA ORIG AMENDMENT
BM

July 26, 2002



GlaxoSmithKline

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation IV
Attn: Document Control Room
Food and Drug Administration
Corporate Building / HFD-520
9201 Corporate Boulevard
Rockville, MD 20850

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JUL 29 2002
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**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets
Response to FDA Request/Comment**

RECEIVED
JUL 31 2002
MEGA/CDER

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for *Augmentin XR™* (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

At this time we are submitting a response to a request for information from Dr. Charles Cooper regarding four (4) patients who participated in Augmentin XR Study 547. The submission includes the documents listed in the table below, in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999).

Folder	Filename	Contents
N050785/	responses.pdf	Responses to questions concerning 4 patients in study 547 received via secure e-mail on July 16, 2002
N050785/	microbiology procedures.pdf	Microbiology procedures for the central laboratory in Study 547
N050785/	multiple isolates.pdf	Procedure for analysis of 2 pathogens of the same genus and species from the same patient at the same visit

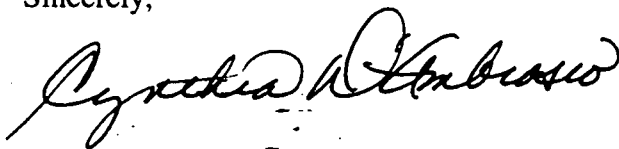
ORIGINAL

Folder	Filename	Contents
N050785/	repeat testing.pdf	Results of repeat culture and susceptibility testing of isolates obtained for baseline blood specimen from patient 547.213.08698
N50785/crf/547	246/009054.pdf 213/008698.pdf	Requested case report forms
N50785/clinstat/	update_Item_8F.pdf	Updated information for patients included in Item 8.F Other Information.

In summary, this submission provides information regarding the designation of pathogens for patients 547.246.009054 and 547.213.008698, the case report forms (CRFs) for these patients and clarification of pathogens isolated and their sources for patients 547.145.19110 and 547.541.25025. The latter two patients were included in Item 8.F. Other Information in the March 29, 2002 resubmission. Updated information for these patients, as well as the other two patients whose information was included in Item 8.F, is provided herein.

This information is being provided in electronic format in duplicate – an Archival copy and a desk copy for Dr. Charles Cooper. Copies of these files also were provided to Drs. Cooper and Samanta via secure e-mail. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.
Director
U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)
Desk copy (1 CD-ROM): Dr. C. Cooper (HFD-520)
Desk copy – cover letter only: Dr. S. Samanta (HFD-520)

NDA ORIG AMENDMENT

BL



GlaxoSmithKline

August 8, 2002

AUG 09 2002

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Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation IV
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AUG 13 2002

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**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets
Commercial Container Labels**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for *Augmentin XR™* (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline. Reference also is made to GSK's responses (submitted on September 14, 2001) to a request for CMC-related information from the Division (dated July 30, 2001).

The purpose of this submission is to clarify the proposed immediate container labels for the commercial packages of *Augmentin XR™*. The NDA proposes two commercial packages - bottles of 28 extended release tablets and bottles of 40 extended release tablets. Item 2.B of the March 29, 2002 NDA resubmission unfortunately contained outdated commercial container labels from the original NDA submission. The labels had been revised during the initial review period and included in the September 14, 2001 submission. The revisions incorporated the current proposed proprietary name, *Augmentin XR™*, and the dosage form designation, Extended Release Tablets. The latter change was made in response to a comment contained the Division's July 30, 2001 request for information relating to CMC aspects of the application.

The labels provided herein contain three additional changes: 1) the layout was changed to accommodate the bar code requirements of the current manufacturing equipment, 2) the dosage was revised to be consistent with the proposed package insert, i.e. "2 tablets every

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Janice Soreth, M.D.

August 8, 2002

Page 2

12 hours" instead of _____ and 3) the text "28 Tablets" was moved lower to be consistent with the placement on the larger volume bottle.

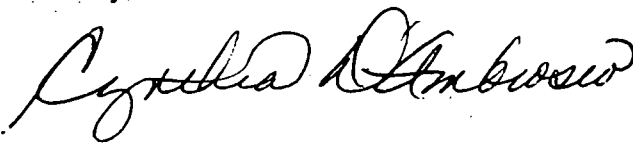
The labels are provided in Portable Document Format provided on a single CD-ROM in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999):

Folder	Filename	Contents
N050785/labeling	container.pdf	Proposed labels for commercial containers

Copies of these files also were provided to Dr. Samanta via secure e-mail for use by the Division's Review Team.

I apologize for any inconvenience that this oversight might cause. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.

Director

U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)

Desk copy of cover letter: Dr. J. Soreth (HFD-520)

Desk copy of cover letter: Dr. S. Samanta (HFD-520)

**APPEARS THIS WAY
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NDA ORIG AMENDMENT

N-000/B1



GlaxoSmithKline

August 23, 2002

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Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
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AUG 28 2002

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**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium)
1000 mg/62.5 mg Extended Release Tablets
Response to FDA Microbiology Reviewer's Request**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for *Augmentin XR™* (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

Please find enclosed a response to a request for information from Dr. Joel Unowsky received via secure e-mail on August 9, 2002. The response provides the penicillin and amoxicillin/clavulanate MICs for over 1400 *Streptococcus pneumoniae* isolates obtained at screening in 27 clinical studies sponsored by GSK over the past 5 years. In addition, graphical comparisons of the penicillin MICs versus the amoxicillin component of the amoxicillin/clavulanate MICs for these isolates are provided. As requested, the graphs display the current breakpoints for amoxicillin/clavulanic acid and the proposed breakpoints for Augmentin XR. The analysis shows good agreement between the penicillin MICs and the amoxicillin/clavulanic acid MICs. The penicillin and amoxicillin/clavulanic MICs tend to be within +/- 1 dilution of each other. This result and the bacteriologic success rates of 94% and 100% demonstrated for Augmentin XR at penicillin and amoxicillin/clavulanic acid MICs of 4 mcg/mL, respectively, support the proposed labeling statements.

ORIGINAL

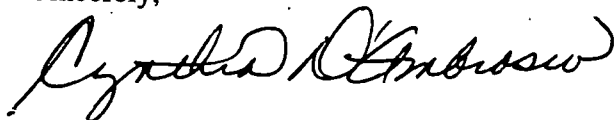
Janice Soreth, M.D.
August 23, 2002
Page 2

This submission is provided in electronic format on a single CD-ROM in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). The folder and file structure is described in the table below.

Folder	Filename	Contents
N050785	response_23aug02.pdf	Penicillin and amoxicillin/clavulanic acid MICs for <i>S. pneumoniae</i> isolates from clinical studies over past 5 years – listing and graphical comparisons.

A copy of the file above was provided to Drs. Unowsky and Samanta via secure e-mail for use by the Division. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.
Director
U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)
 Desk copy of cover letter: Dr. J. Soreth (HFD-520)
 Desk copy of cover letter: Dr. S. Samanta (HFD-520)

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August 27, 2002



GlaxoSmithKline

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
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**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium)
1000 mg/62.5 mg Extended Release Tablets
Response to FDA Biopharmaceutics Reviewer's Comments**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham's New Drug Application (NDA 50-785) for Augmentin XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to your Division on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline (GSK). Please note that documentation within current submissions may refer to either organization.

Reference also is made to our amendments to NDA 50-785, specifically an update on drug stability submitted on August 23, 2001 and a complete response to CMC questions on September 14, 2001.

Additional reference is made to an electronic communication from Dr. Susmita Samanta of FDA to Cynthia D'Ambrosio of GSK Regulatory Affairs on March 6, 2002. Included in that communication were proposed specification limits sent by Dr. Zheng of the Biopharmaceutics Division regarding both amoxicillin release and clavulanate dissolution in Augmentin XR™ Extended Release Tablets. The March 29, 2002 NDA resubmission addressed all of the questions and comments put forth in the March 6, 2002 electronic communication.

Specific reference is made to an electronic communication dated August 9, 2002, containing a set of CMC comments raised by Dr. Zheng of the Biopharmaceutics Division, in conjunction with the review of NDA 50-785.

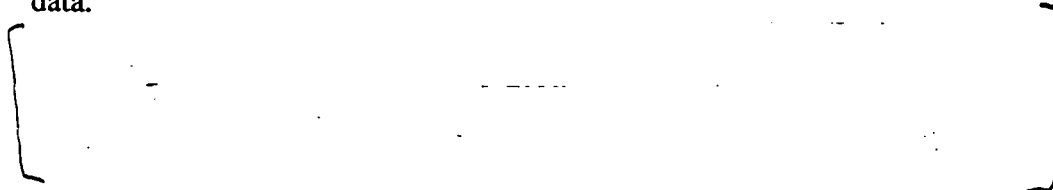
Submitted herein are complete responses to all comments contained within the August 9, 2002 electronic communication. For the Division's convenience, each comment has been reproduced below in bold with the corresponding response provided immediately thereafter.

GSK Responses to CMC Comments from FDA Biopharmaceutics Reviewer

- Q1. The Agency recommends to set a dissolution specification at 3 hours. This 3 hour time point is more appropriate than the 2 hour dissolution time point for the following reasons:**
- i. The second peak in the amoxicillin plasma concentration vs. time profile, which reflects the absorption of amoxicillin from the sustained release layer, occurs at approximately — postdose, which is closer to the 3 hour-dissolution time point than the 2-hour time point.**
 - ii. The 2-hour dissolution time point is in the relatively "flat" or "plateau" region of the dissolution profile when the release of amoxicillin from the sustained release layer has not yet started. In contrast, the 3-hour dissolution time point would more adequately reflect the release from the sustained release layer.**
- A. GSK agree that three-hour, rather than two-hour test point and limits be set for routine quality control. GSK also agrees to the following limits, being identical to those suggested by Dr. Zheng of the FDA in the electronic communication of March 6, 2002:**

NLT — AND NMT — in 3 hours

In the light of these limits GSK will operate a 12 month shelf life for this product, pending the Division's agreement. It is GSK's view however that these limits can be revised, taking account of biopharmaceutical performance and relevant batch data.



GSK's proposed specification for routine QC testing of amoxicillin drug release is summarized below

Amoxicillin Drug Release Specification for Augmentin XR Tablets

Time Point	Minimum	Maximum
1 hour	—	—
3 hours	—	—
6 hours	—	—

- 1. Dissolution data should be provided for 18-month tablet stability batches since the proposed expiration date is — months.**
 - A.** Dissolution profiles generated at the 18 month test point did not include a three-hour measurement, as these were not then included in the testing specification. Full profiles were generated at 12 and 24 months and these were submitted to the Agency (see March 29, 2002 resubmission). These data are adequate for reviewing performance against the 12 month shelf life now proposed by GSK.

3 hour data will be collected routinely in future at all test points in stability studies and reported to the Agency in an appropriate manner.
- 2.1. It was observed that the dissolution pattern changed for the 24-month stability batches. Compared with dissolution pattern for initial testing, the release from the sustained release layer for the 24-month stability batches was slower. Please provide the explanation for this observation.**
 - A.** The slower rates of amoxicillin release at 24 months do not readily correlate with change in other measured quality parameters. Losses of amoxicillin were minimal-to-non-existent. Hence, the slower release rates cannot be ascribed to chemical degradation of the amoxicillin. The slower rates were evident at all sampling points, suggesting that the behavior may not be solely associated with the extended release layer. Neither was there any association with batch, pack type or numbers of units per pack (HDPE containers). At this point, therefore, it is not possible to ascribe a specific cause of the decrease in amoxicillin release rate. GSK are working to establish the cause and, when elucidated will provide to FDA. Amoxicillin release rates of tablets stored for 12 months (proposed shelf life) hardly changed relative to initial values.

Augmentin 875/125 mg Tablets have also exhibited similar, albeit more modest, slowing of dissolution rates for amoxicillin during storage (Reference Annual Report for amoxicillin/clavulanate potassium (q12h) Tablets; NDA 50-720 April 11th 1997; Appendix 7; p000183-000210.)

2.2. Discuss how the changes would affect the in vivo absorption/oral bioavailability of amoxicillin.

- A.** Amoxicillin release rates in stored samples slowed progressively over time. This was most noticeable at the later sampling points and longer storage periods (12, 18 and 24 months). However, the reduction was not great, being in the region of about 10% in samples stored for 12 months at 25°C/60%RH.

The changes are not expected to affect biopharmaceutical performance because the batch of tablets used in the key Phase I study (Study 558) was also used in two other Phase I studies (25000/553 and 25000/583) when tablets up to 10 months old were used.

Table 1: Pharmacokinetic Studies Conducted on Augmentin XR Tablets

Batch	Manufacture Date (Tablets)	Study	Study Period	Age (of tablets)	C.max (mcg/mL)	AUC (0-inf) (mcg.hr/mL)	Time above 4 mcg/mL (hours)
B99012	Aug-99	25000/558	Aug-Sep 1999	Fresh	17.4	75.6	6.0
B99012	Aug-99	25000/553	Jan-Mar 2000	6-8 months	17.9	77.3	6.2
B99012	Aug-99	25000/583	Apr-Jul 2000	8-10 months	15.5	60.8	5.4

The across-study comparison of data in Table 1 shows no trends suggesting that pharmacokinetic performance is influenced by time of storage over a period approximating to the shelf life now being claimed (12 months). The ostensibly lower values for Study 583 can hardly be ascribed to a time effect because the tablets used were comparable in age to those used in Study 25000/553 where pharmacokinetic parameters were very similar to those seen in Study 25000/558.

- 2.3. If available, please provide human pharmacokinetic data resulting from the oral administration of Augmentin XR tablets that have been stored for longer than 12 months.**

A. ☐

3. Please provide the dissolution data for clavulanate acid.

Dissolution profiles for the clavulanate component are provided in Table 2 for batches that were utilized in pivotal Phase I studies and in the Phase III Clinical Trials.

Table 2: Clavulanate Dissolution Profiles in Key Clinical Batches

Batch	Use	% Labeled Clavulanic Acid Dissolved							
		15 mins		30 mins		45 mins		60 mins	
		%	% RSD	%	% RSD	%	% RSD	%	% RSD
B99012	PK Studies 25000/553, 558 & 583	20.6	15.7	51.4	13.5	85.9	10.7	95.3	3.3
B99012	Phase III Clinical Trials	20.6	15.7	51.4	13.5	85.9	10.7	95.3	3.3
B99015	Phase III Clinical Trials	44.1	34.9	86.2	20.2	94.1	12.7	96.5	4.7
B99017A	Phase III Clinical Trials	30.5	23.2	75.3	8.7	92.5	2.5	93.5	1.9
				69.1	12.6			93.0	1.7
B00022A	Phase III Clinical Trials	21.3	22.2	59.6	13.9	88.8	6.5	94.7	1.7

It can be seen that, apart from B99015, none of the batches utilized in the Phase I and III studies would meet the limit proposed by the Agency (Q= — in — minutes). In particular, it can be seen that the — minute value for Batch B99012, which was used in the Pivotal Phase I study, and in Phase III trials was well below the — limit proposed by FDA.

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The limit proposed by GSK ($Q = \text{---}$ in 60 minutes) is more appropriate in the light of performance of these pivotal batches. A 60 minute sampling point ensures that the majority of the clavulanate is monitored and affords better method precision (lower RSD) than do other time points. Table 3 contains clavulanate dissolution profiles for key batches used during development (Phase I and Phase III trials, stability studies and process scale-up studies).

Table 3: Dissolution Rates (Clavulanate) on freshly manufactured Batches

Batch	15 min	30 min	45 min	60 min
B99012	20.6	51.4	85.9	95.3
B99015	44.1	86.2	94.1	96.5
B99017A	30.5	75.3	92.5	93.5
B99017B	48.7	87.0	94.9	95.6
B99017C	47.4	84.8	91.7	92.1
B00003A	41.2	83.0	94.5	95.3
B00003B	50.4	88.9	93.7	93.7
B00003C	43.3	84.7	92.9	93.9
B00004A	43.4	80.7	93.8	94.9
B00004B	51.4	88.8	95.1	95.7
B00004C	52.6	91.1	94.7	95.1
B00022A	21.3	59.6	88.8	94.7
Mean	41.2	80.1	92.7	94.7
% CV	27.0	15.4	3.0	1.3
S.D.	11.1	12.4	2.8	1.2
95% CI Lower Limit	19.0	55.4	87.2	92.3
95% CI Upper Limit	63.5	104.8	98.3	97.1
99% CI Lower Limit	7.8	43.0	84.4	91.1
99% CI Upper Limit	74.7	117.2	101.1	98.3

If a test point other than one hour were to be utilized for routine control, the specification would have to reflect the variation at that sample time. A limit at the --- minute timepoint would need to take account of the wider variation and associated confidence limits. Furthermore, no data are available on the effect of storage on release rate at --- minutes. A --- minute sampling point was not employed in stability studies, sampling being aligned with 30 and 60- minute sampling to monitor amoxicillin dissolution. Dissolution rates, at 30 and 60 minutes are

provided in Table 4 for all measurements performed during stability studies, representing 308 data points at 60 minutes and 100 data points at 30 minutes.

Table 4: Statistics for Clavulanate Dissolution Rates from Stability Studies

	30 min	60 min
Mean	85.3	94.0
% CV	10.9	1.7
Minimum	—	—
Maximum	—	—
S.D.	9.3	1.6
95% CI Lower Limit	66.8	90.9
95% CI Upper Limit	103.9	97.2
99% CI Lower Limit	57.5	89.4
99% CI Upper Limit	113.2	98.7

The spread of data at the 30-minute sampling point is comparable to that seen as in Table 3. The measurement at 60 minutes, in contrast, shows little data spread and a specification limit can reflect this.

In summary, there are compelling data showing that, for routine quality control, clavulanate dissolution is best measured after one hour. The limit proposed by GSK (NLT — in 60 minutes) takes account, not only of the spread of data in Table 2, Table 3 and Table 4 but also the known instability of this component, in dosage forms and in solution at 37 °C. Levels as low as 90% of nominal can be obtained after storage and need to be allowed for in the product specification. Additionally, clavulanate stability in solution is such that modest amounts of degradation occur while the dissolution test is being performed. An — limit (Q= — is appropriate in the light of such considerations.

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Janice Soreth, M.D.

August 27, 2002

Page 8

This submission is provided in electronic format on a single CD-ROM in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). A copy of the enclosed responses was provided to Drs. Zheng and Samanta via secure e-mail for use by the Review Team. If there are any questions or clarifications required, please do not hesitate to contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.

Director

U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)

Desk copy of cover letter: Dr. J. Soreth (HFD-520)

Desk copy of cover letter: Dr. S. Samanta (HFD-520)

Desk copy of cover letter: Dr. J. Zheng (HFD-880)

**APPEARS THIS WAY
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August 30, 2002

NDA 50-785 AMENDMENT
BS



GlaxoSmithKline

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
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**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets - Response to FDA Request/Comment: Statistical**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for *Augmentin XR™* (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

Please find enclosed a response to a request for information from Dr. Thamban Valappil received via secure e-mail on August 26, 2002. The response provides a description of the variables used in the NDA analyses of the modifying factors associated with increased risk of penicillin-resistant *Streptococcus pneumoniae* (PRSP) infection in cases of community-acquired pneumonia, as well as an explanation of how the variables were derived. The modifying factors were derived from an American Thoracic Society (ATS) publication: Guidelines for the Management of Adults with Community Acquired Pneumonia, *Am J of Resp and Crit Care Med* 2001; **163**: 1730-1754. The modifying factors for PRSP include: age > 65, beta-lactam therapy within the past 3 months, alcoholism, immune-suppressive illness (including therapy with corticosteroids) and multiple medical comorbidities. The variables used in the NDA analyses are located in the *ats.xpt* dataset that was included in the March 29, 2002 resubmission.

It should be noted that a similar approach was used in the analysis of patients in the *Augmentin XR™* acute bacterial sinusitis (ABS) studies who were exposed to previous systemic antibiotics. Recent use of systemic antibiotics was identified by the Sinus and Allergy Health Partnership (*Otolaryngology-Head and Neck Surgery*, 2000; **123**: S1-S32.) as a modifying factor associated with PRSP infection in patients with ABS. The

ORIGINAL

Janice Soreth, M.D.

August 30, 2002

Page 2

variables used in this analysis are contained in the *antib.xpt* dataset in the NDA resubmission.

This submission is provided in electronic format on a single CD-ROM in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). The folder and file structure is described in the table below.

Folder	Filename	Contents
N050785	ats_dataset_information.pdf	Description of the variables in ATS dataset and their derivation.
N050785	define.pdf	Definition of variables in the ats.xpt dataset.
N050785/pubs	american_thoracic_society_2001.pdf ewig_1999.pdf sinus_and_allergy_health_partnership_2000.pdf	Publications relevant to the identification of modifying factors associated with risk of PRSP infection.

Copies of the files above were provided to Drs. Valappil and Samanta via secure e-mail for use by the Division. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.
Director
U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)

Desk copy - cover letter: Dr. Janice Soreth (HFD-520)

Desk copy - cover letter: Dr. Susmita Samanta (HFD-520)

Desk copy - cover letter: Dr. Thamban Valappil (HFD-725)

September 6, 2002

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GlaxoSmithKline

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NDA ORIG AMENDMENT
BC

**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets - Response to FDA Request/Comment: CMC**

Dear Dr. Soreth:

Reference is made to SmithKline Beecham Pharmaceutical's (SB's) New Drug Application (NDA 50-785) for *Augmentin XR™* (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg Extended Release Tablets, originally submitted to the Division of Anti-Infective Drug Products on December 20, 2000 and resubmitted on March 29, 2002. SmithKline Beecham Pharmaceuticals is a wholly owned subsidiary of GlaxoSmithKline.

Please find enclosed a response to a request from Dr. Shrikant Pagay received by telephone on August 28, 2002 for information on the current specifications for drug substances contained in Augmentin XR. The request is listed below in bolded text followed by the response.

Request:

Please provide: 1) the current specifications for amoxicillin trihydrate and clavulanate potassium, 2) the location of the information in the DMF(s), and 3) the shelf life and re-test periods for amoxicillin trihydrate and clavulanate potassium.

Response for amoxieillin trihydrate:

GSK is currently approved for sourcing amoxicillin trihydrate for all Amoxil and Augmentin products from two GSK sites, Worthing, UK [DMF — , last annual report update January 18, 2002] and Singapore [DMF — last annual report update March 29, 2002].

DUPLICATE

_____. Also, Singapore amoxicillin trihydrate was used in all qualification batches of Augmentin XR.

The relevant pages from DMF _____ (Annual Report of March 29, 2002) containing the specifications, re-test period and expiration dating for amoxicillin trihydrate are provided in Attachment 1.

In addition, on June 3, 2002 a Supplement - CBE was submitted to all currently approved Amoxil and Augmentin NDAs to formally add an impurity specification for amoxicillin trihydrate, and thereby tighten controls. Please note, all Amoxil and Augmentin NDAs/AADAs to date have been approved without formal impurity limits for amoxicillin trihydrate in accordance with the CFR and now USP. The impurity limit proposal sent to the Agency on June 3, 2002 is in line with the European Pharmacopeial (Ph.Eur.) monograph where acceptable amoxicillin trihydrate impurity limits have been defined. Please see Attachment 2 for copies of the DMF amendment to DMF _____ submitted May 31, 2002 and the sNDA-CBE dated June 3, 2002 sent to all currently approved Amoxil and Augmentin NDAs.

Also, to aid in clarifying this for the Agency a copy of the current Singapore amoxicillin trihydrate specification incorporating these limits is included in Attachment 3.

Response for clavulanate potassium:

GSK is currently approved for sourcing clavulanate potassium for all Augmentin products from two GSK sites, Worthing, UK [DMF _____ last Annual Report update December 3, 2001] and Irvine, UK [DMF _____, last annual report update December 14, 2001]. Clavulanate potassium is shipped to our Bristol, TN drug product manufacturing plant as _____ for use in the Augmentin XR product.

[_____]
Also, Irvine, UK clavulanate potassium was used in all qualification batches for Augmentin XR.

The relevant pages from the DMF _____ (Annual Report of December 14, 2001) containing the specifications and re-test period for clavulanate potassium are provided in Attachment 4. Please note that clavulanate potassium has a re-test period only; it does not have a formal expiration period.

[_____]

Janice Soreth, M.D.

September 6, 2002

Page 3

This submission is provided in electronic format on a single CD-ROM in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). The response and attachments contained herein were provided to Drs. Pagay and Samanta via secure e-mail for use by the Division. If you have any questions regarding this submission, please contact me at 215-751-3468 (telephone) or 215-751-4926 (telefax). Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.

Director

U.S. Regulatory Affairs

Copies: Archival (1 CD-ROM)

Desk copy - cover letter: Dr. Janice Soreth (HFD-520)

Desk copy - cover letter: Dr. Susmita Samanta (HFD-520)

Desk copy - cover letter: Dr. Shrikant Pagay (HFD-520)

APPEARS THIS WAY
ON ORIGINAL



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**RE: NDA 50-785;
Augmentin XR (amoxicillin/clavulanate potassium) Extended Release Tablets;
Follow Up to Telecon of September 9 between Dr. Soreth and Dr. Cocchetto**

I appreciate your time on September 9 to share with me the overall status of DAIDP's ongoing review of NDA 50-785, as we work toward an action in late September. Your feedback was particularly helpful in sharing the Division's two main issues with respect to the clinical aspects of this application. These two main issues, as I understand them, are as follows:

1. The draft labeling from GSK (in the Resubmission of March 29, 2002) proposed an INDICATIONS statement in community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS), including *S. pneumoniae* with penicillin MICs of 2 or 4 mcg/mL. Dr. Soreth informed me that GSK has provided reasonable evidence of efficacy in patients with community-acquired pneumonia due to *S. pneumoniae* with penicillin MICs of 2 mcg/mL, but not for isolates with penicillin MICs of 4 mcg/mL. Dr. Soreth stated that this topic must be addressed appropriately in labeling.
2. FDA has reservations about the risk factors for *S. pneumoniae* in proposed patient groups for community-acquired pneumonia in the INDICATIONS AND USAGE section of draft labeling. Specifically, GSK's clinical studies excluded two subgroups of patients (i.e., alcoholics and patients with immune suppressive illness) and specific data were not collected in a third subgroup (i.e., _____). So, Dr. Soreth advised that the Division plans to remove these risk factors from labeling for CAP. (NOTE: We in GSK recognize these aspects of the patient populations in our clinical studies. DAIDP's plan to remove these three risk factors from the draft labeling for community-acquired pneumonia is reasonable and acceptable to us.)

With respect to the overall status of the NDA, Dr. Soreth indicated that the NDA is headed toward an approval action, pending satisfactory agreement on labeling and resolution of any remaining inspectional issue for the data on ABS from Dr. Hendricks. GSK is committed to working with the Division, quickly, to fully address these issues by the action date in late September.

I advised Dr. Soreth that we in GSK were likely to re-state our perspective on the first issue above, namely, whether to include only pneumococcal isolates with penicillin MICs = 2 mcg/mL, or include such isolates with penicillin MICs = 2 or 4 mcg/mL in the INDICATIONS AND USAGE section. We recognize the challenging nature of such a deliberation. Allow us to briefly summarize the evidence, from our perspective. We welcome your feedback, as stated below.

- Evidence in pneumonia: The Resubmission includes direct evidence in 5 cases of CAP due to *S. pneumoniae* with penicillin MIC = 4 mcg/mL; no per protocol cases were collected with penicillin MIC = 8 mcg/mL. Bacteriological eradication (per protocol) at test of cure in clinically evaluable patients was achieved for 4 of 5 patients (80%). Importantly, 2 of these 5 patients (numbers 557.101.11786 and 557.106.11602) had bacteremic pneumococcal pneumonia with both isolates from blood showing a penicillin MIC = 4 mcg/mL; importantly, on-therapy blood cultures were negative in both patients and both cases were clinical successes at test of cure. While we recognize that five cases with penicillin MIC = 4 mcg/mL is limited, the results are consistent with the desired magnitude of efficacy for such isolates, and these results are supported by evidence in acute bacterial sinusitis and pk/pd information, as summarized below.
- Other evidence: Beyond pneumonia, the Resubmission provides evidence of efficacy against *S. pneumoniae* with penicillin MICs = 2 or 4 mcg/mL from (a) clinical trials in acute bacterial sinusitis and (b) pk/pd data related to the design of the product. In ABS, the resubmission provides data on 40 cases due to penicillin-resistant *S. pneumoniae*; 27 isolates had penicillin MIC = 2 mcg/mL, 11 isolates had penicillin MIC = 4 mcg/mL, and 1 isolate each had penicillin MICs = 8 or 16 mcg/mL. Bacteriological eradication (per protocol) at test of cure in clinically evaluable patients was achieved for 40 of 40 patients (100%), including all 11 cases (100%) with penicillin MICs = 4 mcg/mL. With respect to pk/pd data, DAIDP is aware that GSK worked to design Augmentin XR to achieve amoxicillin concentrations above 4 mcg/mL for at least 40% of the dosage interval. The NDA contains the data to show that on average (n = 55 subjects) amoxicillin concentrations remained above 4 mcg/mL for 49% of the dosing interval. Also, the Augmentin XR pharmacokinetic profile demonstrated success in animal models of respiratory infection against strains of *S. pneumoniae* with MICs up to and including 8 mcg/mL.

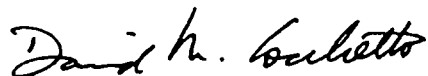
Overall, GSK's view is that the pk/pd profile (taken together with the animal *in vivo* data, substantial *in vitro* data, good clinical success across the proposed indications against a convincing number (37) of evaluable isolates of *Streptococcus pneumoniae* with penicillin MICs = 2 mcg/mL, and good clinical success across the proposed indications against a reasonable number (18) of evaluable isolates with penicillin

MICs ≥ 4 mcg/mL) clearly distinguishes Augmentin XR from the currently available 7:1 formulation. Inclusion of *S. pneumoniae* with penicillin MICs of 2 or 4 mcg/mL in the INDICATIONS statements for CAP and ABS will further reinforce the differences between Augmentin XR and currently available Augmentin products.

The potential for a favorable view by DAIDP on the proposed draft labeling for CAP and ABS due to *S. pneumoniae* with penicillin MIC = 2 or 4 mcg/mL depends on DAIDP's willingness to place substantial weight on the data submitted for patients with acute bacterial sinusitis and the pk/pd data on this product, as opposed to heavy relative weighting on the number of cases of CAP due to isolates with penicillin MIC = 4 mcg/mL. We welcome the Division's feedback on this matter, both as it impacts the decision for labeling for NDA 50-785, and as it will impact our thinking with respect to any future clinical studies on this topic.

This submission is provided in duplicate to NDA 50-785. A desk copy has been transmitted via secure e-mail to Dr. Susmita Samanta for use by the review team. Thank you for your consideration.

Sincerely,



David M. Cocchetto, Ph.D.
Vice President, Antiviral/Antibacterial Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

INTEROFFICE MEMORANDUM

DATE: 9/13/02

TO: Susmita Samanta, M.D.
Project Manager, HFD-520

FROM: Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

THROUGH: Terry S. Peters, D.V.M.
Acting Pharmacology Team Leader, HFD-520

RE: Label for NDA 50,785; Augmentin XR

The intent of this memo is to capture the comments and suggestions from the Pharm/Tox group regarding the label for Augmentin XR, as well as the response from Glaxo-SmithKline (GSK).

On 9/11/02, Dr. Samanta relayed the following comments from Dr. Ellis to the Sponsor via secure email:

"In both the Impairment of Fertility and Teratogenic Effects/Pregnancy sections, they provide a dose multiple for clavulanate that can't be correct if the rats were receiving a 2:1 amox/clav Augmentin formulation and humans taking Augmentin XR are receiving a 16:1 amox/clav formulation. My calculations for the amoxicillin dose ratios are close enough to theirs not to be worth arguing about, but I get a much higher (and more favorable to the sponsor) dose multiple for clavulanate between rat and human than GSK did. They got - and I got about - You might also ask them whether the reproduction studies in mice used the same Augmentin formulation and doses as were used in the rat studies. If the doses were the same for both species, the dose multiples compared to humans using body surface area would not be the same for both species as is implied in the label- the factors used to convert mg/kg doses to mg/m2 doses for rats and mice are not the same."

On 9/12/02, Dr. D'Ambrosio from GSK responded:

"We agree with the observation that the dose multiples for clavulanate should be different numbers for rats versus mice, and propose the following revisions to the draft labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility:

... *Augmentin* at oral doses of up to 1200 mg/kg/day (1.9 times the maximum human dose of amoxicillin and 15 times the maximum human dose of clavulanate based on body surface area) was found to have no effect on fertility and reproductive performance in rats, dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.

Teratogenic effects. Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral doses up to 1200 mg/kg/day revealed no evidence of harm to the fetus due to *Augmentin*. In terms of body surface area, the doses in rats were 1.6 times the maximum human oral dose of amoxicillin and 13 times the maximum human dose for clavulanate. For mice, these doses were 0.9 and 7.4 times the maximum human oral dose of amoxicillin and clavulanate, respectively. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The dosing multiples quoted in the revised text are based on the following calculations:

Conversion of mg/kg/day to mg/m²/day

- For a human dose of 4000mg/day of amoxicillin. This is 80 mg/kg/day for a 50kg person. Multiply by a conversion factor of 37 to get 2960 mg/m²/day.
- For a human dose of 250 mg/day of clavulanic acid = 185 mg/m²/day.
- For a rat dose of 1200 mg/kg/day Augmentin = 800 amoxicillin + 400 clavulanic acid. Multiply by conversion factor of 7 to get 5600 mg/m²/day and 2800 mg/m²/day respectively. This equates to margins over maximum human dose of 1.9 for amoxicillin and 15 for clavulanic acid.
- Conversion factor for pregnant rat is 6 to give margins over humans of 1.6 for amoxicillin and 13 for clavulanic acid.
- Conversion factor for pregnant mouse is 3.4 to give margins of 0.9 and 7.4.

The pharmacologist finds GSK's proposed labeling revisions to be acceptable.

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Amy Ellis

9/13/02 11:33:33 AM

PHARMACOLOGIST

Labeling revisions proposed by the Sponsor are acceptable.

Terry Peters

9/17/02 06:24:42 AM

PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

Samanta, Susmita

From: Stephen.M.LoCastro
Sent: Monday, September 30, 2002 5:53 PM
To: SAMANTAS@cder.fda.gov
Cc: Sharon.M.Maglennon@gsk.com
Subject: Question on NDA 50-785 Drug Product Specification

Dear Susmita,

Our site at Bristol has requested clarification on the final specification for clavulanate dissolution for Augmentin XR Tablets (NDA 50-785). In our proposal to the Biopharmaceutics Division, we had requested:

"Q — in 1 hour"

The final spec received from Biopharmaceutics was:

"NLT — in 1 hour"

The site QA personnel at our Bristol facility have requested clarification as to whether Biopharmaceutics agrees with "Q —" as this may be interpreted differently from "NLT —". It is important for the site to be clear about this as they are preparing to issue release Certificates of Analysis and they need to be sure that they are reporting against the correct specification limits.

Would you be able to contact the Biopharmaceutics reviewer and clarify?

Thanks very much,

Steve

*Steve LoCastro
Assistant Director
Post Approval Regulatory Affairs, Antibiotics
GlaxoSmithKline Pharmaceuticals
Phone: (610) 917-5856
e-mail: Stephen_M_LoCastro*

**APPEARS THIS WAY
ON ORIGINAL**

10/1/02

September 18, 2002

RECEIVED

SEP 19 2002

CDR/CDER



GlaxoSmithKline

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation IV
Attn: Document Control Room
Food and Drug Administration
Corporate Building / HFD-520
9201 Corporate Boulevard
Rockville, MD 20850

GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

Tel. 215 751 4000
Fax. 215 751 3400
www.gsk.com

RECEIVED

SEP 23 2002

MEGA/CDER

NDA ORIG AMENDMENT

BL

RE: NDA 50-785;
Augmentin XR (amoxicillin/clavulanate potassium)
Extended Release Tablets;
Other: Revised Draft Labeling in Response to FDA's Feedback of
September 13 and 17, 2002

Dear Dr. Soreth:

Reference is made to NDA 50-785 under active review in your Division. Please also refer to the communications (via secure e-mail) of September 13 and 17, 2002 where Dr. Susmita Samanta provided the Division's feedback to GSK as revised draft labeling for *Augmentin XR*™ Extended Release Tablets. The purpose of this submission is to respond in full to this important feedback. We are providing our comments in this way in the interest of affording you and your colleagues the opportunity to consider our perspective and discuss this information within DAIDP in advance of our upcoming teleconference.

Teleconferences

We appreciate Dr. Samanta's effort and willingness of the review team to reserve time on the calendar for two teleconferences between DAIDP and GSK to discuss and resolve any remaining items as this application approaches its action date. Please note that we have the following dates and times reserved for these teleconferences:

Thursday, September 19	1:30 to 3:00 p.m., Eastern Time
Monday, September 23	11:00 a.m. to 1:00 p.m., Eastern Time

We look forward to these opportunities to discuss this application.

ORIGINAL

FORMAT OF THIS SUBMISSION

It may be helpful to summarize our approach to this draft labeling. In the enclosed document, we show FDA's text (as provided on September 13 and 17) as "base copy" and all suggested changes from GSK are shown with revision marks using the track changes feature of MSWord. In addition, we have inserted continuous line numbers throughout the document; hopefully, these line numbers will be available to cite to assist the dialogue in the teleconferences.

From GSK's perspective, in this week prior to the Division's target date for action on this application, we continue to strive to achieve the Division's approval of this application, with mutually acceptable labeling, in September 2002. To this end, we have divided our comments on the Division's revised draft labeling into two groups: (1) a group of comments focused on three specific content issues that are very important to GSK in this labeling and (2) some "housekeeping" topics that require minor editing or clarification through discussion with the Division. Obviously, we anticipate that the bulk of our time on the teleconferences will address the first group of topics. All of our comments in this letter are referenced to the specific line numbers in the revised draft labeling. Please note that the data referred to in this response includes patients enrolled by Dr. Hendrick (center 223) in Study 592, because we continue to believe that the veracity of this data are supported by our monitoring of this investigator, and were not fundamentally questioned by FDA's inspectional observations; we understand that further discussion with your Division and the Division of Scientific Investigations may be necessary to attain a shared understanding.

WITHHOLD 6 PAGE (S)

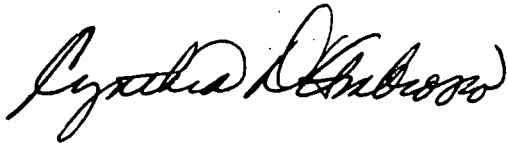
Draft

Labeling

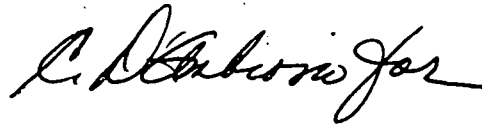
Janice Soreth, M.D.
September 18, 2002
Page 9

We appreciate the Division's consideration of the comments provided above, and we look forward to receiving your feedback at our upcoming teleconference. This submission is provided to NDA 50-785 in electronic format on a single CD-ROM, in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). A copy of this submission was sent via secure e-mail to Dr. Susmita Samanta for use by the review team. Please contact Cindy D'Ambrosio at (215)-751-3468 for any matters regarding this application. Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D.
Director
US Regulatory Affairs



David M. Cocchetto, Ph.D.
Vice President

enclosures: revised draft labeling

**APPEARS THIS WAY
ON ORIGINAL**

Samanta, Susmita

From: Cynthia A. D'Ambrosio
Sent: Monday, September 23, 2002 2:15 PM
To: samantas@cder.fda.gov
Subject: NDA 50-785 - additional labeling requests

Dear Susmita,

Please find below newly revised draft labeling for discussion at our teleconference later this afternoon. The version below is based on the version of September 20th, and it also incorporates the following additions:

- line 36 - corrected molecular formula for clavulanate potassium ($C_8H_8KNO_5$), as per Dr. Pagay's comment
- lines 534-538 - noted additional difference between Augmentin XR and Extended Release Tablets and immediate release Augmentin Tablets: "In addition, the Extended Release Tablet provides an extended time course of plasma amoxicillin concentrations compared to immediate release Tablets."

The file below provides revised figures in the text and table in the Clinical Studies section, ABS subsection (see highlighted numbers), based on the Division's request to remove patients enrolled by Dr. Hendrick in Study 551, as well as Study 592.

In addition, we checked the chemical names for amoxicillin trihydrate and amoxicillin sodium against the listings in the USP dictionary of USAN names (see file below), as requested by Dr. Pagay, and found the names in the draft labeling to be accurate.

Finally, although the clinical success rates in the current draft labeling reflect the Division's re-classification of patient 592.219.19918 as a clinical failure, we are providing a copy of a Data Query Request (DRQ) that confirms the investigator's original assessment of this patient's outcome for further consideration by the Division. A brief description of the patient's course and explanation of the DRQ is also included.

I hope that these documents facilitate the discussion at our teleconference later this afternoon. Please contact me, if you have any problems accessing these documents.

Sincerely,
Cindy

Cynthia D'Ambrosio, Ph.D.
US Regulatory Affairs
GlaxoSmithKline
215-751-3468 (phone)
215-751-4926 (fax)

**APPEARS THIS WAY
ON ORIGINAL**

9/23/02

WITHHOLD 5 PAGE (S)

NDA ORIG AMENDMENT

BL



GlaxoSmithKline

September 24, 2002

Janice Soreth, M.D., Director
Division of Anti-Infective Drug Products
Center for Drug Evaluation IV
Attn: Document Control Room
Food and Drug Administration
Corporate Building / HFD-520
9201 Corporate Boulevard
Rockville, MD 20850

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SEP 24 2002

CDR/CDER

GlaxoSmithKline
U.S. Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA
19101-7929

Tel. 215 751 3868
Fax. 215 751 4926

RECEIVED

SEP 25 2002

MEGA/CDER

**Re: NDA 50-785; AUGMENTIN XR™ (amoxicillin/clavulanate potassium) 1000 mg/62.5 mg
Extended Release Tablets**

Other: Revised Draft Labeling in Response to FDA's Feedback of September 23, 2002

Dear Dr. Soreth:

Reference is made to SmithKline Beecham's New Drug Application for *Augmentin XR™* (amoxicillin/clavulanate) Extended Release Tablets (NDA 50-785) currently under active review in your Division, and to the proposed draft labeling provided to Dr. Susmita Samanta via secure e-mail on September 23, 2002. SmithKline Beecham is a wholly owned subsidiary of GlaxoSmithKline (GSK).

The purpose of this submission is to provide revised draft labeling based on the discussion between representatives of the Division of Anti-Infective Drug Products (DAIDP) and GSK at our teleconference on September 23, 2002. The revised draft labeling is provided as clean running text, with no revision marks. The enclosed draft labeling incorporates the changes that were agreed at the teleconference referenced above in the following lines:

- Description - lines 26 and 36
- Microbiology - lines 128-134, and 139-143
- Indications and Usage - lines 261-264
- Dosage and Administration - lines 523-524, 531, 533-535 and 538-539
- How Supplied - lines 559-560
- Clinical Studies - lines 595, 603-604 and 610-611.

Please note that, as agreed at the teleconference, the enclosed labeling text does not include language previously proposed by GSK in Dosage and Administration regarding

However, it does contain a correction to the spelling of "xanthan gum" in line 45, and

ORIGINAL

Janice Soreth, M.D.
September 24, 2002
Page 2

"(90%)" was changed to "(≥90%)" in lines 132 and 133. The latter change is consistent with the recommended text for this subsection in the FDA's most recent draft guidance (Draft Guidance for Industry. Developing Antimicrobial Drugs — General Considerations for Clinical Trials. Food and Drug Administration, July 1998, page 41.) We also acknowledge the Division's advice that the changes noted above in the How Supplied section are still under discussion within FDA.

This submission is provided to NDA 50-785 in electronic format on a single CD-ROM, in accordance with FDA Guidance for Industry – Providing Regulatory Submissions in Electronic Format (IT3, January 1999). A copy of this submission was sent via secure e-mail to Dr. Susmita Samanta for use by the review team. We not only appreciate the two recent opportunities to confer with the Division via teleconference on the draft labeling for Augmentin XR, but also the open and productive discussion and the timely responses that the Division provided to our proposals. For any outstanding matters regarding this application, please contact me at (215)-751-3468. Thank you.

Sincerely,



Cynthia D'Ambrosio, Ph.D
Director
U.S. Regulatory Affairs

enclosure: revised draft labeling

APPEARS THIS WAY
ON ORIGINAL

Samanta, Susmita

From: Cynthia A. D'Ambrosio
Sent: Tuesday, September 24, 2002 11:49 AM
To: SAMANTAS@cder.fda.gov
Cc: pagays@cder.fda.gov
Subject: NDA 50-785 - further response to 23Sep fax from Dr. Pagay
Importance: High

Dear Susmita,

I sent a message yesterday requesting clarification from Dr. Pagay regarding the proposed limit for _____ in bulk amoxicillin sodium and the proposed specifications for amoxicillin release and clavulanate dissolution from the drug product. In his 23Sep02 fax, he also requested concurrence/commitment on some additional items. At this time, I can confirm GSK's concurrence with or commitment to the following:

- shelf life of the drug product of 12 months from the date of manufacturing
- expiration date for amoxicillin sodium of _____ months when stored at 25°C/60%RH
- commitment to _____

Finally, Dr. Pagay requested that we change the text "2 tablets..." to "Take 2 tablets..." on the commercial bottle labels and the matchbook covers for the physician samples. GSK agrees to make this change; however, we would like to request that, for the physician samples only, this change be introduced at the next printing after product launch. Matchbook covers for the physician samples have been produced, and patients will also receive the commercial containers in order to complete their treatment regimen. If Dr. Pagay would like to discuss this with me, please ask him to contact me at his earliest convenience. Thank you.

Sincerely,
Cindy

Cynthia D'Ambrosio, Ph.D.
US Regulatory Affairs
GlaxoSmithKline
215-751-3468 (phone)
215-751-4926 (fax)
cynthia_a_dambrosio

**APPEARS THIS WAY
ON ORIGINAL**

9/25/02

Samanta, Susmita

From: Cynthia.A.D'Ambrosio@gsk.com
Sent: Tuesday, September 24, 2002 4:28 PM
To: SAMANTAS@cder.fda.gov
Subject: Re: FW: NDA 50-785

Susmita,

I can confirm that the specifications for amoxicillin release and clavulanate dissolution from the Augmentin XR drug product provided in your fax dated September 16, 2002 are acceptable to GSK. For ease of reference, a copy of the fax is provided below.

Sincerely,
Cindy

Cynthia D'Ambrosio, Ph.D.
US Regulatory Affairs
GlaxoSmithKline
215-751-3468 (phone)
215-751-4926 (fax)

"Samanta, Susmita" <SAMANTAS@cder.fda.gov>

24-Sep-2002 14:31

To: Cynthia A D'Ambrosio

CC:
Subject: FW: NDA 50-785

Cindy,

Please see Dr. Zheng's comment.

Thanks

Susmita

-----Original Message-----

From: Zheng, Jenny J
Sent: Tuesday, September 24, 2002 2:26 PM
To: Samanta, Susmita
Cc: Colangelo, Philip M
Subject: FW: NDA 50-785

Susmita,

Would you please confirm with the sponsor that the FDA proposed dissolution specification is in agreement with the sponsor? Thanks.

Jenny

9/25/02

Samanta, Susmita

From: Stephen.M.LoCastro@
Sent: Tuesday, September 24, 2002 5:07 PM
To: pagays@cder.fda.gov
Cc: samantas@cder.fda.gov; Sharon.M.Maglennon@gsk.com; Cynthia.A.D'Ambrosio@gsk.com; Thomas.J.Carr@gsk.com
Subject: URGENT: Registered Specifications for NDA 50-785

Dear Dr Pagay,

In order to ensure that there is no confusion regarding the final, agreed specifications for amoxicillin sodium and Augmentin XR Tablets (NDA 50-785), I've attached a table which includes the specifications for each as we understand them. I'm highlighting three issues which we need to be clear on for our own understanding:

1) As mentioned in a previous contact from Cindy D'Ambrosio, in the amoxicillin sodium specification, you proposed a limit of — for — whereas we had proposed a limit of —. It is important to know whether this was your intention or a typographical error as our batch analysis data does not support the lower limit. None of the batches presented in the NDA would have passed that specification limit.

2) For amoxicillin sodium, we've noted that your proposed specification only referred to analytical methods from our Worthing site, whereas we had listed Worthing and Piscataway as sites of commercial manufacture for this drug substance. Our attached table lists the methods from both sites as originally presented in the NDA.

3) For drug product, you have proposed two methods for impurity analysis:

— This is in line with our proposal, as are the limits. However, we have noted (as was proposed in the NDA) that the — test is meant for release testing, while the — test is meant for shelf-life testing. The different limits for total impurities listed for each — for — and — for — are meant to reflect this difference. Please let us know if you concur with this.

Due to the limited amount of time remaining until the action letter is issued, please contact either Sharon Maglennon [610-964-7904] or myself [610-917-5856] as soon as possible tomorrow morning if you have any issues which need to be discussed.

Kind regards,

Steve

*Steve LoCastro
Assistant Director
Post Approval Regulatory Affairs, Antibiotics
GlaxoSmithKline Pharmaceuticals
Phone: (610) 917-5856
e-mail: Stephen_M_Locastro@gsk.com*

**APPEARS THIS WAY
ON ORIGINAL**

9/25/02

Samanta, Susmita

From: Zheng, Jenny J
Sent: Tuesday, October 01, 2002 4:41 PM
To: Samanta, Susmita
Cc: Colangelo, Philip M
Subject: RE: Question on NDA 50-785 Drug Product Specification

Susmita,

It should be Q — in 1 hour.

Jenny

-----Original Message-----

From: Samanta, Susmita
Sent: Tuesday, October 01, 2002 3:08 PM
To: Zheng, Jenny J; Colangelo, Philip M
Subject: FW: Question on NDA 50-785 Drug Product Specification
Importance: High

Could you please clarify this question from GSK?

Thanks

Susmita

-----Original Message-----

From: Stephen.M.Locastro [mailto:Stephen.M.Locastro]
Sent: Monday, September 30, 2002 5:53 PM
To: SAMANTAS@cder.fda.gov
Cc: Sharon.M.Maglennon@gsk.com
Subject: Question on NDA 50-785 Drug Product Specification

Dear Susmita,

Our site at Bristol has requested clarification on the final specification for clavulanate dissolution for Augmentin XR-Tablets (NDA 50-785). In our proposal to the Biopharmaceutics Division, we had requested:

"Q — in 1 hour"

The final spec received from Biopharmaceutics was:

"NLT — in 1 hour"

The site QA personnel at our Bristol facility have requested clarification as to whether Biopharmaceutics agrees with "Q= —" as this may be interpreted differently from "NLT —". It is important for the site to be clear about this as they are preparing to issue release Certificates of Analysis and they need to be sure that they are reporting against the correct specification limits.

10/2/02

Would you be able to contact the Biopharmaceutics reviewer and clarify?

Thanks very much,

Steve

Steve LoCastro
Assistant Director
Post Approval Regulatory Affairs, Antibiotics
GlaxoSmithKline Pharmaceuticals
Phone: (610) 917-5856
e-mail: Stephen_M_Locastro@gsk.com

**APPEARS THIS WAY
ON ORIGINAL**